Register of Epoch-Making Biologics Hits 10 Years

BY SARA FREEMAN

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE BRITISH SOCIETY FOR RHEUMATOLOGY

BRIGHTON, ENGLAND – The arrival of biologic agents for the treatment of rheumatic disease has been hailed as a groundbreaking event, with their practical use undoubtedly aided by the setup and success of large-scale biologics registers in Europe.

"I think we've been very privileged in the past 10 years to have lived through an era where, rather similar to the introduction of steroids, a truly epoch-making set of drugs have come to the fore," said Dr. David Isenberg. "They have really changed the way we practice in a way that was unimaginable 15 years ago."

Dr. Isenberg, who recently stepped down as the chair of the BSRBR (British Society for Rheumatology Biologics Register) Steering Committee, added that "one very important aspect of the way in which these new drugs have been introduced is the growth of the biologics registers, which have been developed to monitor their use."

Started in 2001, the BSRBR has now become the largest of the European biologics registers, with data still being collected on more than 20,000 participants with rheumatoid arthritis, of whom around 15,000 are receiving anti–tumor necrosis factor–alpha agents.

A year after the register started, the U.K. National Institute for Health and Clinical Excellence (NICE) published guidelines on the use of biologics and recommended that all patients who start treatment with the new agents should be included in the BSRBR.

"Almost immediately, the number of patients recruited per month increased – almost exponentially," said Dr. Deborah Symmons, one of the two principal investigators for the BSRBR.

In fact, it was more difficult to recruit the comparison cohort of patients with active RA who were being treated with nonbiologic disease-modifying antirheumatic drugs (DMARDs) and were anti-TNF naive.

Dr. Symmons, professor of rheumatology and musculoskeletal epidemiology at the Arthritis Research UK Epidemiology Unit at the University of Manchester (England), noted, "It's the only study I've ever been involved with where we massively exceeded our sample size in less than the time that was estimated."

With the recent call for clinicians to start registering patients who are being treated with certolizumab (the latest anti-TNF to gain NICE approval in the United Kingdom), the BSRBR continues to increase its patient numbers. The addition of tocilizumab and abatacept to the register is also planned in the near future.

In addition to the large patient numbers and power of the data that can be generated, the key to the success of the BSRBR is its ability to evolve and change with the times. When the register was started, the primary aim was to see if anti-TNF agents increased the risk of cancer (specifically non-Hodgkin's lymphoma) relative to nonbiologic DMARDs. Additional goals were added over the years, and – to enable long-term comparisons of all drugs in the register – an extended follow-up of all treatment arms was announced just last year.

The BSRBR is one of the few biologics registers to include a control arm of the standard therapy of the time (nonbiologic DMARDs). Because of changing baseline characteristics and anti-TNFs themselves becoming established therapy, however, recruitment into a second, anti-TNF cohort arm has just begun. Patients who start treatment with one of the older anti-TNF agents included in the register (infliximab, etanercept, or adalimumab) are eligible for inclusion into the new cohort. Newer agents entering the register will then be compared with the anti-TNF control cohort.

"Registers are epidemiologic cohort studies dedicated to pharmacovigilance and real-life effectiveness," commented Dr. Angela Zink, one of the key people behind the 13,000-patient German biologics register RABBIT (Rheumatoid Arthritis Observation of Biologic Therapy), which also includes a control arm.

Dr. Zink, deputy director of the German Rheumatism Research Centre and professor of epidemiology of rheumatic diseases at the Charité Medical University Berlin, observed that biologics registers were "long-term enterprises," with payback only many years after their initial setup.

"In the end, registries allow you to answer questions that you couldn't answer with other types of studies," Dr. Zink noted. Indeed, about one-third of patients in RABBIT would not have been eligible for clinical trials and, without the register, would not have been treated with anti-TNFs, she observed.

Without the buy-in of the large pharmaceutical companies that make biologic agents, however, the registers would be impossible to run. Although the BSRBR is funded through the BSR, which in turn has six separate contracts with the relevant manufacturers of biologics in the United Kingdom, the German register has managed to develop a single, seven-way contract with all manufacturers in Germany.

"At the end of the day it works because everyone benefits," he said. The companies essentially get 5 years of follow-up data on their products while the researchers are able to publish their findings in the top rheumatology journals. In addition, "the BSR gets the kudos of running the world's largest biologics register."

The BSRBR is funded by a grant from the BSR. The BSR receives funding from Abbott Laboratories, Biovitrum/SOBI, Merck Sharp & Dohme, Pfizer, Roche, and UCB. This income finances a separate contract between the BSR and the University of Manchester that runs the BSRBR. All decisions concerning data analysis, interpretation, and publications are made autonomously of any industrial contribution. Dr. Isenberg and Dr. Symmons declared that they had no personal conflicts of interest. Dr. Zink has received research grants from Abbott, Amgen, Bristol-Myers Squibb, Essex Pharma, Pfizer, Roche, and UCB. ■

Family Study Identifies Possible Factors Involved in RA

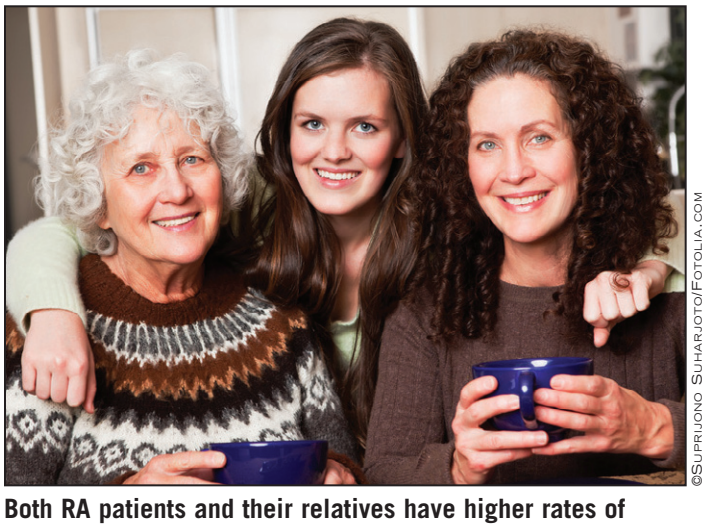
BY SHARON WORCESTER

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

Unaffected first-degree relatives of patients with rheumatoid arthritis have an increased number of known risk factors for RA, compared with unaffected controls. However, the prevalence of risk factors in relatives does not equal that seen in patients, according to Dr. Lotta Ljung, senior consultant rheumatologist at Umeå (Sweden) University Hospital.

For example, the unaffected relatives had a significantly greater prevalence of anti–CCP (cyclic citrullinated peptide) protein IgG, IgA, and IgM antibody isotypes and rheumatoid factors of IgM and IgA isotypes than did the controls, Dr. Ljung said at the meeting, noting that she was not involved in the research. She gave the presentation for researcher Lisbeth Ärlestig, Ph.D., a student at Umeå University, the scheduled presenter who was unable to attend.

The findings could lead to better understanding of the factors that affect rheumatoid arthritis (RA) development. Because the etiology of RA is still unknown and autoantibodies are common in patients affected with RA (and the anti-CCP antibodies discussed appear to be involved in the pathogenesis of the disease), it is of interest to analyze the prevalence, concentrations, and pattern of antibodies in first-degree relatives in multicase families, according to Dr. Ljung. The lead author was Dr. Solbritt Rantapää Dahlqvist, also of Umeå University.



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Both RA patients and their relatives have higher rates of carriage of certain genetic biomarkers than do controls.

The investigators set out to evaluate serologic risk markers for the development of RA in relation to genetic and environmental risk factors. They compared serologic findings in RA patients, unaffected relatives, and healthy controls.

The researchers found that in 196 individuals with RA and 156 first-degree relatives from 61 multicase families compared with healthy controls, respectively, the median concentrations of the anti-CCP isotypes were 237.0 AU/mL and 2.1 AU/mL vs. 1.5 AU/mL for IgG anti-CCP; 3.4 AU/mL and 1.0 AU/mL vs. 0.6 AU/mL for IgA anti-CCP; and 53 AU/mL and 28.5 AU/mL vs. 18.5 AU/mL for IgM anti-CCP. The median concentrations of rheumatoid factors were 134.5 mcg/mL and 5.2 mcg/mL vs. 3.3 mcg/mL for IgM RF and 8.3 mcg/mL and 1.4 mcg/mL vs. 1.0 mcg/mL for IgA RF.

The investigators also found that RA patients were significantly more often SE (shared-epitope) positive than were unaffected relatives (73.1% vs. 53.6%; *P* less than .001), but had similar rates of carriage of the PTPN22t variant (47.7% vs. 45.4%).

Both patients and relatives had the variant at higher rates than did controls. Thus, it appears that SE is more important for the development of RA than is the PTPN22t variant, they said.

"The environmental factor of smoking was also more common among the patients and is shown to be an important risk factor" in univariate but not multivariate analysis, they noted.

Indeed, 58% of patients, compared with 46% of relatives, were smokers. Also, IgG and IgA anti-CCP were significantly associated with SE in the patients, but not in the relatives.

Overall, the RA patients had more risk factors for RA than did the relatives (median, four vs. three; *P* less than .001).

The vast majority of RA patients (93%) had at least three risk factors, whereas only about half (53%) of the relatives had at least three risk factors. Risk factors were defined as anti-CCP antibodies, RF, SE, PTPN22t variant, smoking, and age.

The investigators said they had no relevant financial disclosures. ■